January 14, 2005

J. Lawrence Robinson
President
The Color Pigments Manufacturers Association, Inc.
300 North Washington Street
Alexandria, VA 22314

Dear Mr. Robinson:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for methyl acetoacetate posted on the ChemRTK HPV Challenge Program Web site on February 24, 2004. I commend The Color Pigments Manufacturers Association, Inc. for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Association advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Donald Rodier, Acting Chief of the HPV Chemicals Branch, at 202-564-7633. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Methyl Acetoacetate

Summary of EPA Comments

The sponsor, the Color Pigments Manufacturers Association, Inc., submitted a test plan and robust summaries to EPA for methyl acetoacetate, CAS No. 105-45-3, dated December 29, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 24, 2004.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The submitted data are adequate for the purposes of the HPV Challenge Program.

2. Environmental Fate. The submitter needs to provide measured hydrolysis data for this chemical. The submitter needs to provide more information about the biodegradation of this chemical or provide measured biodegradation data following OECD Guideline 301.

3. Health Effects. The submitted data are adequate for acute, repeated-dose, reproductive and developmental toxicity, and gene mutation endpoints for the purposes of the HPV Challenge Program. Some additional information is needed in the robust summaries.

EPA reserves judgement on the adequacy of the chromosomal aberrations data pending receipt of additional study details. If these details are not available, then *in vitro* chromosomal aberrations testing is needed, with special attention to pH changes.

4. Ecological Effects. The submitted data are adequate for ecological effects endpoints for the purposes of the HPV Challenge Program. Some additional information is needed in the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Methyl Acetoacetate Challenge Submission

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program.

Stability in water. The submitter provided estimated hydrolysis values of 14.1 days at pH 8, and 140.6 days at pH 7. These data do not span the guideline-specified pH and temperature ranges. The submitter needs to provide measured hydrolysis data following OECD Guideline 111.

Biodegradation. The submitter provided the results of a Modified Zahn-Wellens inherent biodegradability test. Inherent studies such as this that show considerable degradation of the parent compound are not adequate for the purposes of the HPV Challenge Program. Challenge Program submitters need to provide ready biodegradation data following OECD Guideline 301 or similar methods. The submitter did provide the results of a biological oxygen demand (BOD) test. EPA cannot determine the adequacy of the BOD test data provided without more information, such as inoculum (adapted or nonadapted), test medium, and method used. If the information is unavailable, then the submitter needs to provide measured ready biodegradation data.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitted data are adequate for the acute, repeated-dose, reproductive and developmental toxicity, and gene mutation endpoints for the purposes of the HPV Challenge Program. The submitter needs to address some deficiencies in the robust summaries.

Genetic toxicity - chromosomal aberrations. The robust summary for the chromosomal aberrations study did not include sufficient details to allow EPA to determine data adequacy. The submitter needs to provide additional details including information on the duration of "short-term incubation," magnitude of responses, the pH minimum observed, and the criteria for cytotoxicity. Sufficient information is needed to determine whether the observed cytotoxicity is the result of the drop in pH or an effect of the test substance. If the pH drop is responsible for the cytotoxicity, the test should be repeated using higher doses with pH adjustment. If the missing information is unavailable, or insufficient to resolve questions about the adequacy of the study, then *in vitro* testing is needed using OECD Test Guideline 473, with pH adjustment and measurement of the pH at the beginning and end of the experiment.

Ecological Effects (fish, invertebrates, and algae)

EPA agrees with the sponsor that adequate data exist for these endpoints. However, the sponsor needs to provide the analytical monitoring procedure used in the fish study.

Specific Comments on the Robust Summaries

Health Effects

Acute Toxicity. The robust summaries for both acute oral toxicity studies need to state the duration of the study and the post-treatment observation period.

Repeated-dose toxicity. The robust summary for the 4-week study needs to state the number of animals/sex/concentration tested, as well as any deviations from OECD TG 407 including whether the heart and spleen were weighed, and whether the spinal cord, intestines, thymus, trachea, uterus, prostate, lymph nodes, and peripheral nerves were histopathologically examined.

Genetic toxicity. The two robust summaries for gene mutation assays are missing details including culture conditions, positive control use, control response, and the statistical methods used. The chromosomal aberrations study summary, in addition to the omissions noted under the test plan comments, lacks information on the specific statistical methods used.

Combined repeated-dose, reproductive, and developmental toxicity. The robust summary for the OECD TG 422 study is missing details including the number of pregnant females per group, schedule of test animal sacrifice, frequency of systemic toxicity measurements, hematology and clinical biochemistry parameters measured, list of organs weighed, number of animals designated for necropsy, specific tissues subjected to histopathological examination, the number of animals designated for organ weight determinations and histopathological examinations, and statistical methods and evaluations.

Ecological Effects

Fish. The robust summary for acute toxicity to fish lacks information on the hardness of the test water.

Invertebrates. The robust summary for acute toxicity to invertebrates lacks information on the hardness of the test water, the loading rate of the daphnids, and the number of daphnids and replicates used.

Algae. Missing study details include concentrations tested, the number of concentrations tested, the number of replicates per concentration, cell concentration measurements, control use and response, signs of toxicity per concentration, test conditions such as temperature, pH, and lighting, and whether analytical monitoring was performed.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.